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## Case-Control Study of Factors Associated With Intrauterine Fetal Deaths

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### Abstract

#### Objective

To study the characteristics of pregnancies that resulted in stillbirth and to determine which may possibly predict intrauterine fetal death (IUFD).

#### Study Design

A total of 161 singleton pregnancies resulting in stillbirth at Nottingham City Hospital from 1991 to 1997 were compared with 499 live births randomly selected from the same period of time. The variables studied were the following: customized birth weight for gestational age, fetal sex, histopathologic cause of IUFD, maternal age, ethnic group, parity, maternal body mass index (BMI), smoking habit, and maternal blood group.

#### Results

In 54.7% of the cases of stillbirth at our institution women presented with reduction or absence of fetal movements before the diagnosis of IUFD. Almost half of the stillbirths (48.4%) were small for gestational age (< 10th percentile) on the basis of gestational age-specific weight. The difference in customized birth weight between stillbirths and live births was statistically significant ( $P < .0001$ ). Increased maternal body mass index (BMI) was positively associated with stillbirth rate ( $P < .001$ ), as was increased maternal age ( $P = .0012$ ). Women with blood group O ( $P = .014$ ) had an even higher stillbirth rate. There was no association between stillbirth rate and maternal ethnic group, maternal smoking, maternal Rhesus status, or fetal sex.

#### Conclusions

This study found that almost half of stillborn babies were small for gestational age. Reduced fetal activity should be investigated thoroughly, with formal measurement of fetal growth as part of this assessment. Maternal blood group and maternal age were found to be important factors in IUFD. Smoking was not confirmed in this study to be a significant factor.

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### Introduction

Intrauterine fetal death (IUFD) remains one of the areas of obstetrics in which improvements could

be made. The major problem facing the obstetrician is the identification of women at risk; as many cases seem to occur in the absence of recognized risk factors.

Although we have some understanding regarding the pathogenesis of IUFD (eg, the role of placental disease), identifying those truly at risk remains problematic. With this in mind, we attempted to identify risk factors associated with IUFD in our population at Nottingham City Hospital.

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## Materials and Methods

Nottingham City Hospital is a busy teaching hospital. About 5700 deliveries are performed yearly at Nottingham's City Hospital. The number of in utero transfers is limited. Between 1991 and 1997 at Nottingham City Hospital, there were 38,697 deliveries and 187 fetal deaths. Of these, 161 stillbirths were singleton pregnancies, for which dates were known. Cases of multiple pregnancy ( $n = 19$ ), termination of pregnancy after the 24th week of gestation ( $n = 1$ ), fetal death diagnosed by ultrasound before the 24th week of gestation ( $n = 2$ ), and those for whom there were no data on the computer system ( $n = 4$ ) were excluded. The included pregnancies ending in stillbirth, which were compared with a control group of pregnancies ( $n = 499$ ) delivered during the same time period, which were selected using random allocation by computer. The number of pregnancies constituting the control group was chosen on the basis of advice from our hospital statistician. Both groups derived from the same geographic population. The computer database had been validated in the past and was shown to be accurate for clinical information in 95% of entries and for delivery information in 99.9%, as the computer record is used to generate the birth certification.[1]

Data relating to pregnancy and maternal characteristics were retrieved from the computerized database. Postmortem reports whenever available were retrieved from the patient case notes. The following maternal characteristics were examined: ethnic origin, weight, height, age, parity, smoking, and blood group. Smoking habit was classified as smoker or nonsmoker, according to the information provided at the first antenatal appointment (usually at 14 to 18 weeks' gestation).

Fetal factors were birth weight, sex, and gestational age. The weight-for-gestation percentile was calculated using the software package GROW (Gestation Related Optimal Weight) Version 1.0, October 1995. This program calculates the percentile position of fetal weight relative to the optimal fetal weight determined on the basis of knowledge of ethnic group, maternal weight at booking, maternal height, parity, and gestational age.

In 92 cases (57.1%) of stillbirth, a postmortem investigation was carried out after delivery. Factors thought to be important in prediction of stillbirth were examined by univariate analysis (Chi square, Yates corrected and Mann-Whitney test, Arcus QuickStat software). This was further examined with logistic regression (SPSS Version 8.0 for Windows).

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## Results

An initial univariate analysis was performed to identify those factors that seemed to be associated with stillbirth. [Table 1](#) (Maternal Characteristics) shows the characteristics for the stillbirth and live birth groups. Maternal age ranged from 16 to 44 years (median age, 29). Mothers in the stillbirth group were slightly older than mothers of live-born infants. There were 30 smokers and 81 nonsmokers; data were not available for 50 women. The control group of live births included 130 smokers and 358 nonsmokers; no data were available for 11 women.

**Table 1**  
Maternal Characteristics

Ethnic origin of the mother was not a factor associated with stillbirth. A slightly higher proportion of women in the stillbirth group were primiparous, but this was not statistically significant.

[Table 2](#) (Fetal Characteristics) shows the differences in fetal characteristics between the 2 groups. The stillborn babies were generally born at an earlier gestational age, as would be expected. One hundred babies (61.7%) were preterm (< 37 weeks gestation) and 61 babies (38.3%) were term. Fifteen fetal deaths (9.2%) were diagnosed after the 41st week of gestation.

Table 2 Fetal Characteristics	
Characteristic	Stillborn (n=161)
Gestational age at delivery (weeks)	34.2 (SD 2.1)
Preterm (< 37 weeks)	100 (61.7%)
Term (≥ 37 weeks)	61 (38.3%)
Diagnosed after 41st week	15 (9.2%)

Calculation of the gestation-specific weight percentiles using the software program GROW showed that half of the fetuses (48.4%) were in the < 10th percentile group. In addition, 61 fetuses (37.8%) were below the 3rd percentile for gestational age. The odds ratios for the percentile groups are calculated using the group 31st-40th percentile as the reference against which all other groups are compared. This group was chosen because it represented the median percentile group for the live born infants. Although a “J” shaped relationship between stillbirth and birth weight percentile has previously been demonstrated,[2] this was not corroborated in our study, as there was no demonstrable increase in stillbirths among larger babies. The extremely strong relationship between stillbirth and poor growth is clearly demonstrated, with stillbirth being much more common in those fetuses in the first 2 percentile groups.

A logistic regression analysis was performed to examine the independent contribution to stillbirth of those characteristics thought to be implicated. Initially, all variables that had a univariate significance of < 0.1 were considered — with parity included, as it is difficult to examine in isolation from the other more significant factors. Body mass index (BMI) was categorized by division into quartiles. Because age showed a very wide distribution, it was divided into quintiles. Blood group was categorized as Group O or other, as blood groups A, B, and AB seemed to confer similar risks in the initial analysis. The only fetal characteristic included in the initial analysis was fetal sex, which appeared to contribute but not quite meet conventional statistical significance on univariate analysis. The other factors thought to be highly significantly associated with stillbirth are pathologic rather than predictive variables (eg, growth restriction profoundly increases the risk of stillbirth), but what we were trying to determine is whether it is possible to identify factors that may help identify women at risk. IUFD will often lead to premature delivery and thus gestational age at delivery is not included.

The results of our analysis, presented in [Table 3](#) (Analysis of Possible Predictive Factors for Stillbirth), can be summarized thus: Women who are older or heavier have a greater risk of stillbirth. Parity, although not significant on univariate analysis, showed in the multivariate analysis that being para 2 was slightly protective against stillbirth. Interestingly, higher parity was not associated with an increase risk of stillbirth when age is taken into account. The effect of blood group is slightly weakened in the multivariate analysis but still shows that women with blood group O have a marginally higher risk of stillbirth. The effect is stronger in the univariate analysis, and given that blood group cannot be influenced by any of the other factors it is likely that this is a real effect.

Table 3 Analysis of Possible Predictive Factors for Stillbirth	
Factor	Odds Ratio (95% CI)
Maternal age (years)	1.05 (1.02-1.08)
Maternal BMI (kg/m <sup>2</sup> )	1.02 (1.01-1.03)
Parity (para 2)	0.95 (0.85-1.05)
Blood group (O)	1.15 (1.05-1.25)

The most common reason for seeking medical attention in the group of women with stillbirth was reduced fetal movement (57.4%). The other common presentations were antepartum hemorrhage (11.1%), abdominal pain or possible labour (18.7%), and hypertension (1.5%). In a surprisingly large number of cases there was no presenting complaint, and the IUFD was diagnosed at a routine antenatal visit, when the fetal heart could not be auscultated (14%).

The vast majority of the stillborn babies appeared to be non-dysmorphic. Postmortem was performed in only 92 (57.1%) of cases. Previously unrecognized fetal abnormalities were found in 7 stillborn babies (7.6% of babies examined; [Table 4](#) (Congenital Abnormalities Found at Postmortem).

Table 4 Congenital Abnormalities Found at Postmortem	
Chromosomal abnormalities	1
Structural abnormalities	6
Cerebral malformations	1
Cardiac malformations	2
Gastrointestinal malformations	1
Genitourinary malformations	1
Skeletal malformations	0
Soft tissue malformations	0
Other	0
Total	7

For cases in which a postmortem was performed, the majority (60, ie, 65.2%) of nondysmorphic fetuses had evidence of probable placental disease, according to postmortem diagnoses that included hypoxia, intrauterine growth restriction (IUGR), placental pathology, placental insufficiency, and meconium aspiration. Abruption was seen in 9 (9.8%) of cases; 2 cases were shown to have suffered an acute fetomaternal hemorrhage; and infection (Group B streptococcus [n=3], Parvovirus [n = 1] and *Streptococcus millerei* [n = 1]) was implicated in 5 cases. In only 9 (9.8%) of postmortems was no cause found.

There was no association between maternal disease and stillbirth rate. The majority of women were low risk. Associated medical disorders included thyroid disease (n=1), essential hypertension (n = 2), sickle cell disease (n = 1), and Turner's syndrome (n = 1). Preeclampsia was present in 1 case and nonproteinuric hypertension in 2 cases.

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## Discussion

In this case-control study, we tried to identify pregnancy features associated with IUFD. We used customized growth charts to calculate the percentile that a particular weight achieved in relation to the expected end point. Determining the birth weight of fetuses that died in utero is a potential problem because of weight loss that can occur postmortem. Therefore, the distribution of birth weights of stillborn babies would artificially be skewed and would falsely increase the odds ratio of growth restriction. However, in our unit, most of the stillborns were delivered soon after diagnosis of fetal death (usually within 24 hours). In a study of fetal histology and stillbirth, it was estimated that 80% of all stillbirths are delivered within 1 week after death.[3] Bias attributed to differences between fetal weight at time of death and weight at the time of delivery is likely to be limited.[4] Almost half of the babies (48.4%) were in the < 10th percentile for gestational age-specific weight and more than a third (37.8%) were below the 3rd percentile. It is evident that poor growth was a factor in many of these cases. The vast majority of IUGR fetuses were not diagnosed clinically during the antenatal period. This is a problem when conventional risk factors for stillbirth are not present. A previous study performed in Nottingham during a similar time frame confirmed that only 17% of fetuses in < 10th percentile group were identified antenatally in a population of women identified as being low-risk at booking.[5]

The reason for referral was recorded in 91 cases. It is interesting that in more than half of the recorded cases (54.7%) the complaint was of reduced or absent fetal movements. Reduced fetal movements can be associated with adverse fetal outcome, and women who report reduced fetal movements should be investigated thoroughly. This should entail clinical assessment of fetal growth and whenever appropriate ultrasonographic assessment of the fetus. It is also of interest that a

proportion of women did not have any complaint at all, with 14% of IUFDs detected on a routine antenatal clinic appointment when the fetal heart was not audible. In addition, 12.5% of women attended with symptoms of labor and fetal heart rate were not present.

Increased BMI was positively associated with stillbirths. The strong correlation of IUFD with high BMI did not seem to be due to fetal macrosomia. It is possible that IUGR is harder to detect clinically in heavier women. We think it is unlikely that we had cases of undiagnosed diabetes in the group of pregnancies that ended in stillbirth as all these women had blood sugar and glycosylated hemoglobin levels measured (after diagnosis of fetal death), and they were within reference range.

Male fetal sex did not reach statistical significance as the confidence intervals crossed unity. Some evidence from previous studies suggests that male fetuses are more likely to suffer from antenatal hypoxia (ante- or intra-partum). Other studies have shown an association of male fetal sex with intra-partum hypoxia ("fetal distress") in terms of low Apgar scores at 5 minutes, low umbilical artery pH, and risk of emergency cesarean section.[6–8] It is possible there is an association between sex of the fetus and risk of stillbirth,[2,9] but it was not statistically significant in our study.

Although stillbirth was not associated with primiparity in this study, it seems that in multiparous women, previous delivery of live birth is a protective feature.[10]

In this study, stillbirth was associated with increasing maternal age. Other studies have suggested that fetal outcome worsens with advancing maternal age.[2,10–12] It is difficult to make recommendations on the basis of age, but ultrasound for fetal growth might help, especially if other risk factors are present.

There were 3 cases of chromosomal aneuploidy (trisomy 21, trisomy 13, and tetrasomy 16). These cases were missed during antenatal screening and were diagnosed at postmortem examination. Invasive testing had not been offered antenatally because the maternal age was 30 years in 2 cases and 31 years in 1 case, and the 16- to 18-week biochemical screening did not show high risk of chromosomal aneuploidy.

In our study, smoking did not increase the risk of stillbirth. This was a surprising finding. The association between smoking in pregnancy and IUGR has been well documented in previous studies; however, this is a dose-dependent effect and contributes only marginally to overall fetal growth. Some studies have also confirmed an association between smoking and risk of stillbirth,[10,12] but others have not.[13] In this study, women were categorized as smokers or nonsmokers according to what they reported at booking. These data were entered by the community midwife, who has a close relationship with the patient, and we think that the data given were accurate at that time. However, we do not have data on the number of cigarettes the women smoked or whether they reduced/stopped smoking following the booking of pregnancy. For this reason, the effect of smoking in these pregnancies may be missed.

Maternal blood group was found to be associated with stillbirth. Maternal blood group O was significantly associated with stillbirth and the risk seems to be decreased for blood groups B and AB. It is difficult to explain the association of certain blood groups with IUFD. Some studies have shown an association between cot deaths and maternal blood group O[14] and association with maternal blood group O and stillbirth.[15] Other work demonstrated an apparent positive association between maternal blood group O and low birth weight and a negative one between maternal blood group AB and low birth weight.[16] The biological mechanism is not known. A possible link between maternal blood group O and increased thrombotic predisposition could offer an explanation, although the data available are still inconclusive.[17]

This study once again has demonstrated the extra information that may come to light with

postmortem examination, with previous fetal abnormalities being seen in 7.6% of cases examined. This highlights the importance of this examination in reaching a true diagnosis after such a tragic event.

### **Conclusion**

There is a strong association between fetal growth restriction and stillbirth. An improvement in the identification of IUGR may improve the outcome for some pregnancies. However, the vast majority of pregnancies complicated by IUFD were apparently low-risk pregnancies in which IUGR was not detected antenatally. Devising strategies to improve detection remains one of the more difficult aspects of antenatal care. Studies entailing the increased use of ultrasound directed at a low-risk group have not shown an improvement in fetal outcome, and other less technological interventions, such as symphysis fundal height measurements, have also failed to deliver widespread improvements in detection.

Pregnancies associated with reduced fetal activity warrant careful assessment of fetal wellbeing and should not be considered as low risk. Cardiotocography in this setting is not helpful, and further measures of fetal wellbeing may be necessary. Certainly in the presence of reduced fetal movements, ultrasound assessment of fetal growth and liquor volume, with further investigation if growth is poor, is justified.

Increased maternal age is associated with higher rates of IUFD. This may become more problematic as an increasing number of women decide to postpone childbearing for social reasons. This is a difficult issue, as there is no age at which the risk becomes definitive, rather there is a gradual increase in risk from the end of the third decade. Assessment of fetal growth with ultrasound in the presence of maternal risk factors may be useful, although we are not aware of any studies to show this. Prospective intervention studies may be warranted.

The postmortem examination showed significant unexpected abnormalities in 5 cases, and in 4 cases postmortem confirmed the ultrasonographic suspicion. Additionally, 8 cases of infection possibly causing IUFD were diagnosed on postmortem examination. Unfortunately, parents opted for postmortem examination only in 57% of the stillbirths. Expert counseling should be offered to the parents regarding postmortem examinations, as they may provide additional data concerning the possible cause of IUFD or alter the management in future pregnancy.

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